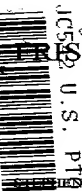


04/07/98



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Pursuant to 37 CFR 1.53(b), transmitted herewith for filing is the CIP Application of application Serial No. 08/835,920, filed April 10, 1997.

Inventor(s): Shu Jun CHENG
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Title: "METHODS FOR TREATING HYPERPLASIA"

Priority Claim (35 U.S.C. 119) is made, based upon:

Japanese Application No. 321195/1996, filed November 18, 1996
 (A certified copy of Japanese Application No. 321195/1996 was filed in parent application SN 08/835,920 on September 15, 1997)

Enclosed herewith are:

- ☒ Specification (Description, Claims, Abstract): Pages 1 - 15; Number of claims 1 - 22
- ☒ CIP Declaration and Power of Attorney (executed)
- ☐ **TO BE POST-FILED: SIGNED DECLARATION UNDER 37 CFR 1.53(f) UNEXECUTED DECLARATION ENCLOSED FOR INFORMATION PURPOSES ONLY**
- ☐ _____ Sheets of drawings, Figures 1 - _____ ☐ Formal ☐ Informal
- ☒ Assignment and Form PTO-1595 Recordation Form Cover Sheet
- ☐ Certified copy (ies) of priority document(s) identified above -- **SEE NOTE ABOVE**
- ☒ Information Disclosure Statement including Form PTO-1449
- ☐ Preliminary Amendment
- ☐ Verified Statement(s) Claiming Small Entity Status
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	Number Filed		Number Extra	Rate		Calculations
Total Claims	<u>22</u>	-20 =	<u>2</u>	x \$22.00 =		\$ <u>44.00</u>
Independent Claims	<u>1</u>	-3 =	<u>-</u>	x \$82.00 =		\$ <u>-</u>
MULTIPLE DEPENDENT CLAIMS				+ \$270.00 =		\$ <u>-</u>
ASSIGNMENT RECORDING FEE				BASIC FEE		\$ 790.00
						\$ <u>40.00</u>
				Total of above Calculations		\$ <u>874.00</u>

To the extent not tendered by check, authorization is given to charge any fees under 37 CFR 1.16 and 1.17 during pendency of the application, or to credit any overpayment, to Deposit Account No. 06-1378. Duplicate copy of this letter is enclosed.

FRISHAUF, HOLTZ, GOODMAN, LANGER & CHICK, P.C.

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METHODS FOR TREATING HYPERPLASIA

The present application is a continuation-in-part application of application Serial No. 08/835,920 filed April 10, 1997.

FIELD OF THE INVENTION

The present invention relates to methods for treating the hyperplasia caused by a papilloma virus, such as *Condyloma acuminata* or genital warts which involves administering an extract of tea containing catechins (*camellia sinensis*).

BACKGROUND OF THE INVENTION

Papilloma viruses comprise a DNA virus which infects epithelial cells of mammals and which causes uncontrolled cell replication. There are many types of papilloma virus which infect human and animal species, but they all can infect the basal epithelial cells and persist in an episome or as DNA integrated into the host genome. The mechanism by which they cause tissue growth may be related to the E4 and E5 proteins they all produce in related forms, which appear to interact with p54 and other host proteins which control the cell cycle. The effects of papilloma virus which have been described include genital warts or *Condylomata acuminata*, common warts, plantar warts, bovine papillomas, and cervical intra-epithelial neoplasia in women.

The detection of human papilloma virus ("HPV") in *Condyloma*

acuminata involve a method of taking a tissue sample or a smear from the infected area and determining the DNA of the virus. According to this method, the detection rate is almost 100%.

Types HPV6 and 11 of the virus are the ones most commonly detected and because HPV16 has been detected in malignant squamous cell carcinoma from cancer of the penis, cancer of the cervix and *Condyloma acuminata*, there is a strong possibility that HPV16 is related to the malignancy of *Condyloma acuminata*.

Means for the treatment of *Condyloma acuminata* caused by human papilloma virus which have been tried include physical means such as surgical excision, electrocauterization, cryosurgery, laser therapy, etc., and medications such as applications of Podophyllin, 5-Fluorouracil, Bleomycin, Interferon, Imiquimod, etc., which are presently available. However, surgical treatment is distressing for the patient, considering the site of infection, and with topical applications there is the concern of side-effects. The aforesaid medications work either by cytotoxic tissue destruction or by enhancing the cellular immune response by causing local inflammation. Accordingly, a conclusive treatment has heretofore not been available.

Condyloma acuminata has a high rate of recurrence, and a complete cure is difficult unless treated constantly. Therefore, a treatment which has a high degree of safety and is convenient is strongly desired.

A treatment of *Condyloma acuminata* or other diseases caused by papilloma virus is desired which would be easy for the patient to take. For example, it would be desirable to have a medication which can be applied to the affected area by the patients themselves and which would provide good results after a relatively short period of use and have no side-effects.

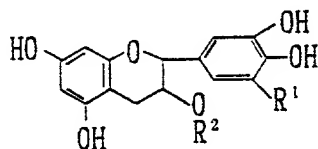
SUMMARY OF THE INVENTION

The present inventors searched for a natural substance which has no side-effects, may be safely applied for a long period of time by the patients themselves and is notably effective. After extensive testing, the inventors discovered that catechin, a component of tea which is an everyday beverage, is effective for treating hyperplasia caused by papilloma virus, and thus the present invention was developed.

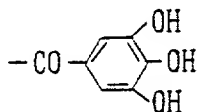
Accordingly, the present invention relates to a method for the treatment of hyperplasia caused by papilloma virus, comprising administering to a human an effective anti-hyperplasia amount of a tea extract containing catechin as a main component. More specifically, the present invention concerns the treatment of *Condyloma acuminata*, common warts, plantar warts and cervical intra-epithelial neoplasia by local administration i.e., topical administration, or oral administration, or a combination of topical and oral administration of tea catechin.

DETAILED DESCRIPTION OF THE INVENTION

The tea catechin for use in the present invention is shown below in the following formula I



wherein R¹ represents H or OH and R² represents H or



The tea catechins are more specifically, epicatechin, epicatechin gallate, epigallocatechin gallate, gallocatechin, etc. (including derivatives thereof). These catechins can be used singly, or two or more may be mixed together. Out of these it is particularly desirable to have (-)-epigallocatechin gallate as a main component. Examples of tea catechin compositions for use in the present invention include the following: POLYPHENON 100™ (produced by Mitsui Norin Co.; Composition: (+)-gallocatechin 1.44%, (-)-epicatechin 5.81%, (-)-epigallocatechin 17.57%, (-)-epicatechin gallate 12.51%, (-)-epigallocatechin

gallate 53.90%; or POLYPHENON E™ (produced by Mitsui Norin Co.; Composition: (-)-epicatechin 10.8%, (-)-epigallocatechin 9.2%, (-)-epicatechin gallate 6.5%, (-)-epigallocatechin gallate 54.8%, (-)-gallocatechin gallate 4.0%).

The tea catechin or tea catechin composition for the treatment of, for example, *Condyloma acuminata*, of the present invention could be used, for example, in the form of an ointment such as a cream, a jelly, or an emulsion; or in the form of a suppository such as a capsule, and usually the tea catechin component is combined with an excipient, an extending agent, an emulsifier, a dispersing agent, etc. Vaseline is suitable as a base for the ointment. For the ointment, the content of tea catechin should be between 2-20% by weight, preferably between 12-18% by weight, and more preferably 15% by weight. In the case of a suppository, the content of tea catechin should be 50-500 mg/capsule, preferably 200-300mg/capsule, or more preferably 250mg/capsule.

A typical usage example for the ointment is to apply the ointment directly to the infected area of the external genital organs or vagina, a vaseline cream containing 2-20% by weight catechin, from once to several times everyday for a period of 1-2 months. A typical usage example for the suppository in the case where, for example, the infected area is the cervix or the vagina, is to insert a capsule containing 50-500mg tea catechin, from once to several times everyday for a period of 1-2 months.

There is no danger of side-effects from the use of tea catechins for the treatment of, for example, *Condyloma acuminata*, since the tea catechins are natural substances derived from tea, which is commonly consumed regularly, and it may be taken for long periods of time. Moreover this medication may be easily applied to or inserted in the infected area by the patients themselves. The composition of the present invention for a treatment of, for example, *Condyloma acuminata*, has a very high potential for practical use.

The tea catechin compounds utilized in the present invention can be administered orally in the form of tablets, capsules, granules, powders or syrups. The pharmaceutical preparations for oral administration can be produced in a conventional manner using adjuvants that are generally known in the art, such as excipients, binders, disintegrating agents, lubricants, stabilizers, corrigents and the like. Although the dosage may vary depending upon the symptoms and age of the patient, the nature and severity of the disease or disorder, in the case of oral administration to an adult human patient, the tea catechin compounds used in the present invention may normally be administered at a total daily dose of from 100 to 2,000 mg, either in a single dose, or in divided doses, for example, two or three times a day.

Examples

The present invention will be explained in more detail with reference to the following examples which are in no way meant to limit the scope of the invention.

Test Example 1

An ointment consisting essentially of a vaseline based vaginal lubricant containing, as the main component, tea catechin (Trade name: "POLYPHENON 100", produced by Mitsui Norin Co. Ltd., its main component: (-)-epigallocatechin gallate) was applied to the cervix of healthy mice (50 mice in a group) in catechin dosages of 8mg, 15mg, and 38mg for a period of 7 consecutive days. After this time, pathological and histological examinations were carried out and it was determined that except for a mild inflammatory reaction in the cervix of the group of mice administered with the 38mg dose, no toxic effect was observed.

Example 1

Clinical tests of the present invention were carried out at the Cancer Institute, Chinese Academy of Medical Sciences in Beijing, China, with a group of 11 women who had been diagnosed with HPV-infected *Condyloma acuminata*. All patients were confirmed to have *Condyloma* in the vulva (external genital organs) and cervix according to clinical examination, cytologic,

colposcopic and pathologic tests. Warts were from 0.2 to 2cm in diameter.

Tests were carried out on these 11 patients using either a vaseline-based ointment containing 10 wt% of tea catechin (Trade name: "POLYPHENON 100", produced by Mitsui Norin co., Ltd., crude catechin content is about 90 weight % and its main component is (-)-epigallocatechin gallate) or using a suppository containing 300mg/capsule of the above tea catechin. Applying the ointment to the external genital organs and applying the suppository to the cervix, the treatments of the present invention were used continuously once a day for about two months.

During the period of treatment, examinations and colposcopic tests of the infected areas were carried out. Results obtained are shown in Table 1. As shown in Table 1 hereinbelow, when the infected area completely disappeared it was judged to be cured, when 50% or more disappeared, it was judged to be improved and when less than 50% or nothing disappeared, it was judged that there was no effect.

Table 1

Infected Area	No. of Patients	Cured	Improved	No Effect
External genital organs	9	4	3	2
Cervix	2	1	0	1

As is evident from Table 1, 7 cases out of 9 (77.8%) of *Condyloma acuminata* of the external genital organ showed a clear effect (being either cured or improved). In one case of the cervical infection, the tumor completely disappeared, and thus was cured. During this period, apart from some patients who experienced slight pain or inflammation in the infected area and a few other patients who felt some itching, there were no obvious side-effects observed.

Example 2

The clinical tests at the Cancer Institute, Chinese Academy of Medical Sciences in Beijing, China were conducted in the same manner as in Example 1, using a vaseline-based ointment containing 15 weight % tea catechin on external and internal warts, with a group of 33 female patients diagnosed with HPV-infected *Condyloma acuminata*. In this group, 8 of the patients were infected in two areas. Results are shown in Table 2 hereinbelow. As is evident from Table 2, 92% of *Condyloma acuminata* of the external genital organs and 70% of the vaginal *Condyloma acuminata* were cured or improved, and in the case of the cervical *Condyloma acuminata*, all cases were cured. 25 cases out of 41 cases showed were cured, and the curing ratio was 61%.

Table 2

Infected Area	No. of Patients	Cured	Improved	No Effect
External genital organs	26	18	6	2
Vagina	10	2	5	3
Cervix	5	5	0	0
Total (%)	41	25 (61.0)	11 (26.8)	5 (12.2)

Example 3

The clinical tests at the Cancer Institute, Chinese Academy of Medical Sciences in Beijing, China were conducted in the same manner as in Example 2, except that the ointment contained 15 weight % of a different tea extract ("POLYPHENOL E", produced by Mitsui Norin Co., Ltd., which is similar to "POLYPHENOL 100"; the crude catechin content of "POLYPHENOL E" is about 82 weight %, and its main component is (-)-epigallocatechin gallate) with a group of 22 female patients diagnosed with HPV-infected *Condyloma acuminata*. Results are shown in Table 3 hereinbelow. As is evident from Table 3, out of 16 cases of *Condyloma acuminata* of the external genital organs, 7 were cured and 6 improved; a total

of 13 (81.3%) being effected. In the case of *Condyloma acuminata* of the vagina, out of 6 cases 3 were cured and 2 were improved; a total of 83.3% was confirmed to be effected.

Table 3

Infected Area	No. of Patients	Cured	Improved	No Effect
External genital organs	16	7	6	3
Vagina	6	3	2	1
Total (%)	22	10 (45.5)	8 (36.4)	4 (18.2)

The entire disclosure of Japanese Patent Application No. 8-321195 filed on November 18, 1996, including the specification, claims and summary, is incorporated herein by reference in its entirety.

WHAT IS CLAIMED IS:

1. A method for treating hyperplasia caused by a papilloma virus comprising administering to a human in need thereof a composition which comprises a tea catechin in an effective anti-hyperplasia amount.

2. The method according to claim 1, wherein tea catechin comprises (-)-epigallocatechin gallate.

3. The method according to claim 1, wherein said composition is in the form of an ointment.

4. The method according to claim 2, wherein said composition is in the form of an ointment.

5. The method according to claim 1, wherein said composition is in the form of a suppository.

6. The method according to claim 2, wherein said composition is in the form of a suppository.

7. The method of claim 3, wherein the tea catechin is in an amount of 2 to 20% by weight.

8. The method of claim 3, wherein the tea catechin is in an amount of 5 to 20% by weight.

9. The method of claim 3, wherein the tea catechin is in an amount of 15% by weight.

10. The method of claim 8, wherein the composition comprises vaseline as a base to form a cream.

11. The method of claim 10, wherein the cream is topically applied to external genital organs.

12. The method of claim 5, wherein the suppository contains 50 to 500mg by weight of the tea catechin.

13. The method of claim 5, wherein the suppository contains 200 to 300mg by weight of the tea catechin.

14. The method of claim 5, wherein the suppository contains 250mg of the tea catechin.

15. The method according to claim 13, wherein the suppository is applied to the vagina of a human.

16. The method of claim 1, wherein the composition is topically applied to an infected area on a human.

17. The method according to claim 16, wherein the infected area is the vagina.

18. The method according to claim 16, wherein the infected area is an external genital organ.

19. The method according to claim 16, wherein the infected area is the cervix.

20. The method according to claim 1, wherein the papilloma virus causes *Condyloma acuminata*.

21. The method according to claim 1, wherein the papilloma virus causes cervical intra-epithelial neoplasia.

22. The method according to claim 1, wherein the tea catechin is orally administered.

APPLICATION FOR UNITED STATES LETTERS PATENT

CIP DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I declare that:

My residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **METHODS FOR TREATING HYPERPLASIA**

the specification of which [X] is attached hereto:

[] was filed _____, as Application Serial No. _____.

I have reviewed and understand the contents of the above-identified specification, including the claims.

I claim priority benefits under 35 USC §119 of: (i) any foreign application(s) for patent or inventor's certificate listed below; or (ii) any United States provisional application(s) listed below; and have also identified below any foreign application(s) for patent or inventor's certificate, or PCT international application having a filing date before that of the application(s) on which priority is claimed.

COUNTRY	APPLICATION NUMBER	DATE (day, month, year)	PRIORITY CLAIMED
Japan	321195/1996	18-11-1996	yes <u> X </u> no _____
			yes _____ no _____
			yes _____ no _____
			yes _____ no _____

I hereby claim the benefit under 35 USC §120 of the prior application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in a manner provided by the first paragraph of 35 USC §112, I acknowledge the duty to disclose information which is material to the examination of this application including material information which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application in accordance with 37 CFR 1.56(a).

08/835,920
(Application Serial No.)

April 10, 1997
(Filing Date)

pending
(Status)
(patented, pending, abandoned)

(Application Serial No.)

(Filing Date)

(Status)
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I appoint the following attorneys to prosecute this application and to transact all business in the U.S. Patent & Trademark Office connected therewith: Stephen H. Frishauf, Reg. No. 16,233; Leonard Holtz, Reg. No. 22,974; Herbert Goodman, Reg. No. 17,081; Thomas Langer, Reg. No. 27,264; Marshall J. Chick, Reg. No. 26,853; Walter J. Baum, Reg. No. 20,641; and Richard S. Barth, Reg. No. 28,180, Douglas Holtz, Reg. No. 33,902; and Robert P. Michal, Reg. No. 35,614.

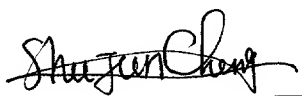
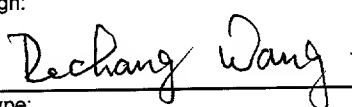

APPLICATION FOR UNITED STATES LETTERS PATENT

CIP Declaration and Power of Attorney

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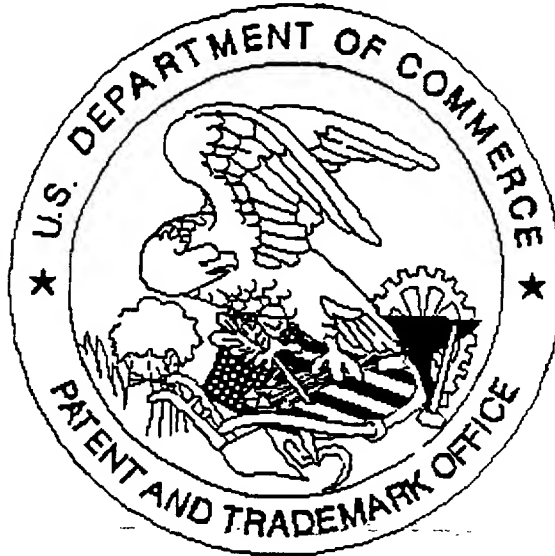
COUNTRY	APPLICATION NO.	FILING DATE	*PATENT OR **PUBLICATION NO.	DATE
Japan	321195\1996	Nov. 18, 1996		
Europe	97120182.7	Nov.18, 1997		
Canada	2221370	Nov.17, 1997		
Australia	44438/97	Nov.10, 1997		
Korea	60940/1997	Nov.18, 1997		
Taiwan, R.O.C.	86115494	Oct.21, 1997		
Republic of China	97122670.9	Nov.17, 1997		

ABSTRACT OF THE DISCLOSURE

A method for a treatment of hyperplasia caused by papilloma virus, such as for treating *Condyloma acuminata* which comprises administering tea catechin. Tea catechins do not involve the risk of side-effects and may be easily applied to or inserted in the infected area by the patients themselves.

United States Patent & Trademark Office

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